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Making Evolutionary Biology a Basic Science for Medicine

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Abstract (244 words)

New applications of evolutionary biology in medicine are being discovered at an accelerating rate, but few physicians have sufficient educational background to utilize them fully. This article summarizes suggestions from several groups who have considered how evolutionary biology can be useful in medicine, what physicians should learn about it, and when and how they should learn it. Our general conclusion is that evolutionary biology is a crucial basic science for medicine. In addition to established evolutionary methods and topics, such as population genetics and pathogen evolution, the article also highlights questions about why natural selection leaves bodies vulnerable to disease. Knowledge about evolution provides physicians with an integrative framework that links otherwise disparate bits of knowledge. It replaces the prevalent view of bodies as machines with a biological view of bodies shaped by evolutionary processes.

Like other basic sciences, evolutionary biology needs to be taught both before and during medical school. Most introductory biology courses are insufficient to establish competency in evolutionary biology. Premedical students need evolution courses, possibly ones that emphasize medically relevant aspects. In medical school, evolutionary biology should be taught as one of the basic medical sciences. This will require a course that reviews basic principles and specific medical applications, followed by an integrated presentation of evolutionary aspects that apply to each disease and organ system. Evolutionary biology is not just another topic vying for inclusion in the curriculum; it is an essential foundation for a biological understanding of health and disease.

One hundred and fifty years after publication of *The Origin of Species*, one might expect that medicine would already have made full use of evolutionary biology. Far from it. New applications of evolutionary biology to medical problems are being discovered at an accelerating rate. The other articles in this special supplement on *Evolution in Health and Medicine* illustrate recent research progress. This article considers what changes in medical education are needed to bring the full power of evolutionary biology to bear most quickly on human health problems. For the sake of focus and simplicity, we here address only medical education; parallel educational recommendations will offer similar benefits in other health sciences, especially public health.

Several sources contribute to the recent flowering of evolutionary approaches in medicine. The first is that the basic science of evolutionary biology continues its rapid development, building on the stable foundation of Darwin and Wallace's theory of natural selection (1). Genetic variants carried by individuals who reproduce more than others tend to increase in frequency over the generations, thus shifting the genetic make up and mean phenotype of the population to be more like them, and generally better adapted to their environments. The role of natural selection in shaping living organisms has been empirically confirmed beyond dispute. Selection is by no means the only factor, however. Mutations are inevitable; DNA is damaged by radiation and toxins, and replication is not perfect. Other random events are also important; genetic drift can push neutral or even deleterious alleles to high frequency, while a storm might eliminate all individuals with a useful mutation. Population bottlenecks, inbreeding, and migrations, also shape gene frequencies, which in turn influence the distribution of phenotypes. Natural selection and these other evolutionary mechanisms change species, and, equally important, keep them the same via stabilizing selection that disfavors individuals with extreme traits (2, 3).

These core principles are, however, only the roots of a rapidly growing network of explanations based on evolution. One main branch is phylogeny. Long-established methods for analyzing relationships within and among species are now being augmented by new methods that use molecular genetic data to test hypotheses about the relationships among populations and species, and about the large scale history of life itself (4). The other main branch is the study of

adaptation. The unity of all life was only one of Darwin's greatest discoveries; the other was his explanation for why organisms have traits that are so well adapted to the challenges they face. No plan is involved; natural selection tends to increase the frequencies of alleles of individuals that survive and reproduce better than others in specific environments (5). Sewall Wright envisioned this process as a landscape of hills and valleys, where the hills represent peaks of fitness and the valleys regions of reduced fitness. Selection tends to move traits up nearby slopes toward fitness hilltops, but nearby higher peaks can be difficult to reach because the transition requires moving through "valleys" of decreased fitness (6).

Tinbergen and Mayr provided an important clarification of the difference between proximate questions about mechanisms and evolutionary questions about origins and functions. (7, 8) They helped biologists recognize that every trait of every organism needs two separate and complementary kinds of explanation, proximate explanations of how mechanisms work, and evolutionary explanations (sometimes called "ultimate explanations") about how they got to be the way they are. For instance, the proximate explanation of the adrenal gland includes its anatomy, tissues, chemical constituents, and the developmental processes that assemble them. Separate, and equally important, is an evolutionary explanation; the phylogeny of the adrenal gland, and how it has conferred a selective advantage. Notice that each kind of question has two sub-questions. A complete biological explanation requires answers to what are now known as Tinbergen's Four Questions: What is the mechanism? How did the mechanism develop? How has it given a selective advantage? What is its phylogeny?

Many advances in evolutionary biology have emerged from asking evolutionary questions about traits important to medicine and public health, and the answers provide advances for medicine; the benefits flow in both directions. Rates of aging are heritable, so why hasn't selection eliminated or at least greatly slowed aging? The strength of selection is weaker at older ages, so deleterious mutations can accumulate, and genes that give advantages in youth will be selected for even if they have pleiotropic deleterious effects later in life (9, 10). Populations with mostly females can have many more offspring than those with an equal sex ratio, so why aren't sex ratios more often female biased? Because parents maximize their reproductive success by making offspring of whichever sex is less common, notwithstanding the penalty to group

success, as RA Fisher recognized long ago (11). Why is reproduction sexual at all, given that nonsexual reproduction is twice as productive? This is a fascinating problem, only partly solved; most proposed solutions attribute it to the advantages of having genetically diverse offspring (12, 13). Reducing the genome to a single copy during meiosis seems wasteful; why not have oocytes that start with many cells? Meiosis and crossing over may have evolved to help minimize the penetration of super-selfish genes that arrange for their own preferential transmission at the expense of other genes and an individual's health (14), as well as to repair damaged DNA sequences. Why is cancer so persistent, and why does its prevalence increase at older ages? The evolutionary answer arises from the limits of selection in eliminating deleterious alleles, from trade-offs with the benefits of tissue repair, and from genetic changes induced by pathogens (15). Why do humans tend to have only one offspring at a time (16)? Why is first reproduction delayed for almost 20 years? Such traits receive evolutionary analysis in life history theory (17, 18). Why do individuals often act in ways that decrease their own survival and reproduction? One reason is that such actions can increase the reproductive success of relatives who have identical genes (19, 20). Another is that investing in mate competition has relatively greater fitness payoffs for males, thus explaining the 300% excess of male vs. female mortality rates at sexual maturity in modern populations (21). Yet another is that our dietary and exercise preferences were shaped in environments fundamentally different from those common now (22). What are the evolutionary reasons for capacities for pain, fever, and negative emotions? Although painful and costly, they are adaptive responses that evolved in conjunction with regulatory mechanisms that express them in situations where they are useful (23, 24).

Investigations into such questions have tested scores of evolutionary hypotheses, many with specific applications in medicine (25-28).

New genetic data and methods

New progress is also made possible by availability of vast amounts of genetic data and associated new methods for generating and analyzing DNA sequence and gene expression data. This is perhaps most obvious in our new ability to use genetic information to trace phylogenies of species, subpopulations, and genealogies of individuals (4). New data and methods also allow estimation of the strength of selection acting at a given locus, allowing us to test

hypotheses about selection in humans (29, 30). For example, strong signals of selection surround the locus of the alcohol dehydrogenase gene in Southeast Asians (31). It is also now possible to test evolutionary theories about differences in selection acting on genes derived from paternal and maternal sources, as in the case of imprinted genes (32). Accurate measurements of mutation accumulation have also become a reality (33); this might enable us to address long-standing questions about the consequences of mutation accumulation or the load of mutations (34). We are only beginning to discover the many ways that genetic data can be used to generate and test evolutionary hypotheses, and the ways that evolutionary theory can guide genetic studies and help to interpret unexpected results (35).

Third, increasing distance from 19th century theories of degeneration and 20th century eugenics makes it easier to recognize the value of modern evolutionary applications in helping individual patients. In the late 19th century, Spencer's ideas were more influential than Darwin's, with detrimental effects on evolutionary biology. In the early 20th century, evolutionary approaches to health emphasized eugenics, supposed racial superiority, and fears of degeneration, exploited by the Third Reich (36). When Nazi horrors were publicized at the end of World War II, scientific publications on evolution and medicine ceased suddenly (37). While associations linger from previous links to eugenics, repudiation of such social policies is now so widely shared that it is easier to recognize the ways that evolutionary biology can help us understand diseases. New evolutionary approaches to medicine are almost entirely unconnected with these earlier movements. Modern approaches tend to distance themselves actively from concerns about races and the species. Instead, they focus on ways that evolutionary biology can help to solve medical problems of individuals and meet the public health needs of communities (37).

Finally, evolutionary approaches are growing in medicine thanks to new publications and broader education of physicians and researchers. Controversy about teaching evolution in public schools continues to inhibit evolution education, but it also has stimulated interest in many of the best students (38). Several recent books on evolutionary approaches to medicine (25, 27, 28, 39, 40) have given rise to many new undergraduate courses on the topic, and recent international conferences have brought together those working in related areas, with predictable synergy (26, 41, 42).

Recommendations about education approaches for evolution in medicine

Despite this progress, few physicians and medical researchers have had a formal course in evolutionary biology, and even fewer have had a chance to learn specific applications in medicine and public health through a course in evolutionary medicine. Many have never even been exposed to the necessity of finding evolutionary as well as proximate explanations. Implementation of recommendations commissioned by the American Association of Medical Colleges and the Howard Hughes Medical Institute (AAMC-HHMI) would help change the situation. Twenty-two leading scientists, physicians, and medical educators met five times from 2007 to 2009 to recommend *Scientific Foundations for Future Physicians* (43). Instead of specific courses, they recommend education that results in eight competencies that should be mastered by students Entering medical education (E 1-8) and eight more for students in the course of Medical education (M 1-8).

E 1-7 correspond roughly to mathematics, scientific methods, physics, chemistry, biochemistry, cell biology, physiology, and facultative adaptations to internal and external changes. E8 is about evolutionary biology. As far as we are aware, this is the first recommendation from a major medical education body that physicians need to master evolutionary biology. The AAMC-HHMI report frames the evolution competency broadly, “Demonstrate an understanding of how the organizing principle of evolution by natural selection explains the diversity of life on earth.” This could include all of evolutionary biology. The specific wording seems to emphasize phylogeny and phenomena at the level of the species and above, however, some especially important medical applications involve how selection shaped traits that allow individuals to adapt to their environments, and the role of evolutionary factors other than selection. A more inclusive global competency could be phrased: “Demonstrate an understanding of how natural selection and other evolutionary processes account for the history of life and the relationships among species, how these processes have endowed organisms with traits that promote reproductive success, and why they leave some aspects of the human body vulnerable to disease.”

The areas E 1-7 are established components of premedical education, so much previous thought has gone into how they can best be taught, augmented by those in the AAMC-HHMI report. Evolutionary biology, however, is just now being recognized as a basic science for medicine. Only a few papers address the issues. Two studies document the absence of evolutionary biology from the medical curriculum (44, 45), and several articles make general recommendations about teaching evolutionary biology in medicine (46-48). This article appears to be the first attempt by a diverse group of scientists to address the question systematically.

Our suggestions are based on discussions by three overlapping groups of authors. Several authors spent 2007-2008 at the Berlin Institute for Advanced Study working together on evolutionary applications in medicine and optimal education strategies. Four authors had extensive discussions in the course of organizing the Sackler Colloquium. Finally, four authors presented papers at the Colloquium on topics related to the role of evolution in medical education. The authors' opinions are, of course, diverse. This report summarizes major areas of agreement, and attempts to clarify some issues on which opinions differ. We recognize that evolution is of equal importance for other health professions, such as nursing, and that it is especially important for public health, however because somewhat different issues arise for each field, we decided to limit our recommendations here to the field of medicine.

The authors generally agree on five general points, summarized in the text box

[text box 1 starts here]

General conclusions and recommendations

1. *Better education about evolutionary biology and its applications in medicine will have substantial benefits for physicians, their patients, public health workers, researchers, and other health professionals.* This conclusion is supported by other articles in this issue, and by explanatory material below in association with specific recommendations.
2. *Much of this education needs to be provided or initiated prior to beginning formal medical studies.* Like mathematics, chemistry, genetics, and the study of biological

mechanisms (proximate biology), evolutionary biology is a basic science that should be taught prior to medical school.

3. *The evolution content in introductory biology courses is insufficient, specialized undergraduate courses are will be important.* The authors hold varying opinions about whether to recommend general overview courses, or courses specialized to the needs of future physicians. All agree that substantial evolution education is essential.
4. *Some aspects of evolutionary biology need to be taught as a part of the medical curriculum, despite the practical challenges.* The medical curriculum is already overly full. However, medically relevant principles of evolutionary biology need to be taught during professional school, just as they are for other basic sciences such as anatomy, genetics, and physiology.
5. *Evolutionary biology is a unifying principle that provides a framework for organizing medical knowledge from other basic sciences.* Attaining a deep understanding of this general framework is a worthy learning objective, because much of the power of evolutionary thinking in medicine comes from its ability to foster integrative thinking about our bodies as products of evolutionary processes.

[text box 1 ends here]

Providing a rationale for evolutionary content in medical education

The relevance of evolutionary biology in medical education is by no means universally recognized. Medical school deans and other educators often ask for evidence that knowledge about evolutionary biology will improve the effectiveness of health care professionals. A simple response is to cite direct applications. For instance, doctors need to understand the evolution of antibiotic resistance, methods for tracing pathogen phylogenies, how selection shaped mechanisms that regulate protective responses such as pain and fever, and the intimate connections between evolution, environment, and diseases of aging. However, limiting the discussion to such direct applications sells short the utility of evolutionary biology in medicine.

Much basic science education in medicine is required, not because it has direct daily applications, but because it is essential for understanding the body and disease. As summarized in Overarching Principle 2 in the AAMC-HHMI report, “The principles that underlie biological complexity, genetic diversity, interactions of systems within the body, human development, and influence of the environment guide our understanding of human health, and the diagnosis and treatment of human disease.” We require competence in calculus, physics and chemistry, not because they are needed every day in the clinic, but because physicians with competence in these areas will better understand the body, and will make better medical decisions.

For instance, most medical schools provide an extensive course on developmental biology because understanding how a zygote develops into an adult organism is an important foundation for understanding the body in general, and deviations related to disease. Understanding how natural selection and other evolutionary processes have shaped the body and its components across evolutionary time is equally valuable. Like developmental biology, it describes patterns of development that explain why the body is the way it is, and why certain aspects leave us vulnerable to diseases. So far, however, no medical school teaches evolutionary biology as a basic science comparable to embryology.

The large scale structure of evolutionary applications in medicine can be organized into ten areas by intersecting the two subfields of evolutionary biology (phylogeny and adaptation), with five different targets of selection: human genes, human traits, pathogen traits, pathogen genes, and somatic cell lines such as those in cancer and the immune system (26). Some of these areas are well developed and extensively taught. For instance, population genetics is the foundation for all evolutionary approaches to disease, and phylogenetic methods are widely applied to pathogen evolution. Others are less well developed. For instance, asking questions about why selection has left the body vulnerable to disease is a newer enterprise that offers methodological challenges, as well as opportunities for deeper understanding (40, 49, 50).

General recommendations like those above provide a foundation for more specific suggestions for what should be taught, when, and how. The AAMC-HHMI report eschews course recommendations in favor of suggesting specific competencies and learning objectives. We

follow this same format, expanding on occasion to illustrate how physicians who master specific learning objectives will practice superior medicine.

Premedical Competencies

Learning objective 1 for the Evolution Competency in the AAMC-HHMI report requires students to be capable of explaining “how genomic variability and mutation contribute to the success of populations.” This is a valuable objective, but its implementation requires sophistication to avoid confusion. The wording could lead some to think that mutations exist in order to speed evolution, or to think that the evolutionary explanation for maintained genetic variation is well understood, when it is actually an issue of intensive study in evolutionary biology, as illustrated by articles by David Houle and Eyre-Walker in this issue (51, 52). Variation is only the raw material; selection does the work, and drift brings added complications. Also, while the success of populations is important, one of the great achievements of 20th century evolutionary biology is recognition that selection generally acts to maximize benefits to individuals and their genes, not species or populations (53, 54). The other learning objective, “Explain how evolutionary mechanisms contribute to change in gene frequencies in populations and to reproductive isolation,” encompasses a breadth of important material. Neither of these learning objectives focuses explicitly on issues of bodily adaptation and maladaptation that are crucial for medicine.

More detailed learning objectives for evolutionary biology would make them more similar to those for other basic sciences. For instance, among the six learning objectives for E3 (physics), students are expected to, “Demonstrate knowledge of the principles of thermodynamics and fluid motion,” and “Demonstrate knowledge of principles of quantum mechanics, such as atomic and molecular energy levels, spin, and ionizing radiation.” With these in mind, we offer several comparably specific learning objectives for evolutionary biology. We recognize that our opinions are no substitute for a representative body of experts convened to address these issues; nonetheless, they may be useful.

1. *Demonstrate an understanding of how natural selection shapes traits in organisms.*

Grasping how selection works turns out to be quite difficult, in part because it requires

replacing intuitive thinking about species-typical normal types with population thinking that views a species as a collection of genetically diverse individuals. It also requires recognizing how evolutionary explanations are different from proximate explanations; instead of describing structures and mechanisms, they describe how a process changes the distribution of characteristics of a population over the generations.

- Describe how the beaks of the many species of finches of the Galapagos have come to be well-matched to the usual foods of each species.
 - Describe the differences between human and chimpanzee teeth and guts and the evolutionary forces that are likely responsible.
 - Describe distinctive aspects of human facial musculature, and the evolutionary forces likely to have shaped them.
 - Show how selection can account for a species staying mostly the same across thousands of generations.
2. Describe the differences between proximate and evolutionary explanations, and the two subtypes under each.
- Provide proximate and evolutionary explanations for the metabolic pathways that synthesize bilirubin.
 - Provide proximate and evolutionary explanations for the retention of fluid in congestive heart failure.
 - Provide proximate and evolutionary explanations for the cessation of sexual cycling in young human females who exercise intensely regularly.
3. Describe the relative roles of mutation, selection, drift, and migration in accounting for genotypes and phenotypes.

- Explain the origins of lactase persistence into adulthood in certain populations, and the factors that explain its current distribution.
 - Discuss the prevalence of blue eyes in different populations, and how you would investigate the various possible evolutionary explanations.
4. Describe the mathematical formulations that describe the rate of change of an allele's frequency under different strengths of selection, and the implications for hypotheses about the role of selection in accounting for differences among human populations.
 - Intestinal lactase persistence has given selective advantages as large as 8% in dairying cultures. Compare this strength of selection to that for other traits.
 - Apply these methods to myopia to conclude whether the recent use of eyeglasses has likely increased rates of nearsightedness.
 5. Explain how the comparative method and other strategies can be used to test evolutionary explanations.
 - High uric acid levels have been hypothesized to give an advantage by slowing rates of aging arising from oxidative damage. How could you use comparative data to assess this hypothesis?
 - A colleague argues that humans evolved to eat only vegetables. Explain how you would use comparative data on teeth and guts of other primates to assess this hypothesis.
 6. Be able to describe the role of tradeoffs in traits shaped by natural selection.
 - Explain why natural selection has not made the head of the radius thicker to protect against fracture.

- What tradeoffs are likely to have shaped mechanisms that regulate fat storage in humans?

7. Understand the core principles of behavioral ecology

- What are the main areas to which a pathogen, such as tapeworm, allocates life effort, and the tradeoffs among them?
- Explain the basic principles of foraging theory in patches, and how these might apply to the distribution of a disease vector.

8. Describe phenomena explained by kin selection, and inclusive fitness more generally.

- Kin selection is said to explain “altruism.” What are some examples?
- A colleague suggests that aging might be valuable for the species to speed evolution. How would you assess this idea?
- Explain how an individual’s actions can influence his or her fitness even after reproduction has ended.

9. Understand sexual selection, and how it can shape sex differences.

- Provide proximate and evolutionary explanations for sex differences in life span.
- Why does oogenesis in females end during fetal life, while spermatogenesis in males continues into old age? What genetic diseases are associated with father’s age?

Such detailed objectives may seem to be asking too much. They are, however, simpler and more directly relevant to medicine than other proposed learning objectives such as the principles of quantum mechanics, and being able to explain how molecular structure is determined by X-ray diffraction. The above list could easily be expanded and refined. We hope others will.

Medical Competencies

The AAMC-HHMI report lists eight competencies to be attained in medical education, including applications of physics and chemistry (M2) and genetics (M3). It does not include any specific applications of evolution. Competency M1 is “Apply knowledge of molecular, biochemical, cellular, and systems-level mechanisms that maintain homeostasis, and of the dysregulation of these mechanisms, to the prevention, diagnosis, and management of disease.” This describes the application of proximate knowledge to the body and disease. A parallel Competency to bring in the evolutionary half of biology, perhaps M1b, would be “Apply knowledge of evolutionary factors that have shaped the body and its regulatory systems to the prevention, diagnosis, and management of disease.”

Possible learning objectives for evolutionary Medical Competencies include:

1. Explain what is meant by facultative adaptation (phenotypic plasticity) and how such adaptations are shaped by natural selection.
 - Explain tanning in response to sunlight
 - Explain the effects of early life experiences of caloric deprivation and stress on later metabolism, and how you would investigate if these effects are facultative adaptations or something else.
2. Explain how to calculate heritability, and what it means.
 - Height is highly heritable, yet genome-wide association studies have so far found no common genetic variants that account for more than a few percent of the variation for height. Explain.
 - Explain why high heritability for a common disease is likely to indicate strong effects of novel environmental factors.
3. Describe why the concept of tradeoffs means that no trait in the body can be perfect.

- A strong immune response would seem to be useful. Explain tradeoffs and other reasons why we remain so vulnerable to infection.
 - A narrow birth canal has serious costs to mother and infant. What evolutionary tradeoffs likely account for the narrowness of the birth canal?
4. Understand the role of modern environments in causing certain diseases.
- The past hundred years have seen an “epidemiological transition” in which chronic disease has come to overshadow acute infectious disease. Describe the responsible chronic diseases, the reasons for this transition, and why our bodies are ill-suited for some aspects of our modern environment.
 - Describe how the rise of agriculture has influenced disease vulnerability, and if there is evidence that agriculture has changed genotypes.
5. Describe how path-dependence makes evolved bodies fundamentally different from designed machines.
- The human spine is a source of much trouble; propose some possible evolutionary explanations.
 - A twisted omentum can cut off blood supply to the gut. Describe the evolutionary reasons for human vulnerability to volvulus, and a comparative test of your hypothesis.
6. Demonstrate understanding of how methods for tracing phylogenies can be applied to genetic data.
- Show how to use genetic data to determine which of several possible pathogen populations is the most likely source of a patient’s infection.

- Describe how genetic data can be used to show our relatedness to other primates.
7. Explain how co-evolution of hosts and pathogens results in arms races that shape traits prone to contribute to disease.
- Streptococcus has evolved with primates for millions of years. Describe a disease complication that may arise from the co-evolution of host defenses and pathogen strategies.
 - Cholera kills by dehydration. Describe the proximate mechanism, and the selective processes likely to have shaped it. Use this information to comment on the likely costs and benefits, for pathogen and host, of using drugs to block this mechanism.
8. Understand how the absence of pathogen exposures can cause disease.
- Why does normal development of the vertebrate gut require the presence of signals from gut bacteria?
 - What are some medical consequences of modern hygiene and antibiotics that eliminate such signals?
 - Describe why the absence of helminths in the human gut is associated with certain diseases.
9. Demonstrate understanding of the processes that shape pathogen virulence and antibiotic resistance.
- Antibiotic resistance can emerge and spread in just a matter of months. Describe the responsible proximate and evolutionary factors.
 - Explain why pathogens spread by vectors such as mosquitoes tend to be more virulent than those spread by respiratory secretions.

- Bacteria from deep soil samples show resistance to many antibiotics. Explain.

10. Describe how the principles of signal detection theory explain how selection shapes mechanisms that regulate defenses such as fever and pain, and how these principles can guide research about when it is safe to use drugs to block such defenses.

- Costs of fever include tissue damage, the risk of seizures, and metabolic costs. Describe how high you would expect these costs to be in comparison with the benefits if fever is controlled by a regulatory mechanism that is near optimal.
- If natural selection shaped optimal regulatory mechanisms, why don't more problems arise from using drugs that block normal defense responses such as cough and vomiting?

11. Understand somatic selection

- Describe how selection among immune cells results in adaptive responses to infection.
- Describe the importance of somatic selection in explaining cancer and in planning chemotherapy strategies.

12. Understand the evolutionary origins of senescence.

- Explain some of the evidence that aging rates are life history traits shaped by selection.
- The physiological reserve declines with age at remarkably similar rates in multiple organ systems. Explain why.
- A colleague says that nothing can be influenced by natural selection after reproduction ends. Why is this incorrect?

13. Explain the origins and significance of genetic variations that influence responses to pharmaceutical drugs.

- What do drug metabolizing enzymes do, and what are the medical consequences of variation in their activity among individuals?
- What was the role of drug metabolizing enzymes in our evolutionary past and why might this have generated the variation we see today?

14. Demonstrate understanding of the aspects of microbial genetics that affect medical outcomes:

- What is the evolutionary significance to an RNA virus of a mutation rate 1000 times greater than that of a DNA virus? What implications does this have for the design of vaccines against HIV and influenza?
- How can DNA be exchanged among bacteria? What is the functional significance for the bacteria? What are the implications for the development of antibiotic resistance?

Once again, we emphasize that the above Learning Objectives and Examples are only suggestions. We hope they will encourage more systematic investigations of optimal policies about evolution education in medicine. We know we have omitted important items, and a sophisticated committee would edit many items to a more suitable format. While we await such more comprehensive assessment, some will ask what specific topics should be covered in the medical curriculum. Remarkably few suggestions have appeared (46, 55). See the text box for topics that should be covered in a medical school course on evolutionary biology.

[text box 2 begins here]

A possible sequence of topics in the medical curriculum

1. A review of core principles of evolutionary biology
2. Common misunderstandings about evolution—how to recognize and avoid them
3. Evolutionary explanations—importance, formulation, testing
4. Cooperation, kin selection, levels of selection

5. Evolutionary genetics, signals of selection, drift, pleiotropy, demography, etc.
6. Evolutionary considerations in epidemiology, and genome wide association studies
7. Life history theory applied to humans
8. Senescence and late-onset diseases
9. Reproduction, sexual selection, and related medical problems
10. Antibiotic resistance and virulence evolution
11. Co-evolution, arms races, and related aspects of infectious diseases
12. The ecology and evolution of emerging diseases
13. Somatic evolution in cancer, and immunology
14. Diseases of modern environments and the epidemiological transition
15. Defenses, their regulation, and their costs
16. Trade-offs, at levels from genes, to physiology, to behavior
17. Development as a product of and contributor to evolutionary change
18. Facultative adaptations (phenotype plasticity) and related diseases
19. Human evolution and ancestral environments
20. Genetic differences among human populations, and rates of evolutionary change
21. Heritability and an understanding of how genes interact with environments
22. Behavioral ecology, behavior, and the origins and functions of emotions

[text box 2 ends here]

The integrative power of evolutionary understanding for medicine

Two things about medical education are widely acknowledged; there is more to learn than anyone can learn, and much of what we teach students now will be obsolete soon. The usual conclusion is that we need to teach students general principles, and we need to teach them how to find specific information when they need it (43).

An evolutionary framework offers a valuable contribution that stretches beyond any specific discipline. It does not address one level, such as biochemistry, or one system, such as the immune system. Rather, it offers principles that apply to every biological system at every level. As a recent overview of another Sackler Colloquium on Darwin noted, “Most scientists agree that evolution provides the unifying framework for interpreting biological phenomena that

otherwise can often seem unrelated and perhaps unintelligible (56).“ It offers a sturdy integrative framework, one on which myriad facts can be hung in retrievable locations. Bilirubin metabolic pathways become much more memorable when integrated with the evolutionary reasons for those pathways. The role of cholera toxin in the small bowel makes more sense when considered in light of factors shaping virulence. The tendency of certain strains of streptococcus to cause rheumatic fever makes more sense when integrated with the arms races that shaped the vulnerability. Proximate mechanisms that explain our vulnerability to obesity and substance abuse make more sense when framed in terms of the environments that shaped those mechanisms.

Beyond a framework for organizing medical knowledge, a deep evolutionary understanding also helps to correct the prevalent dependency on the metaphor of the body as a designed machine (47). Of course, the body is a system of interlocking mechanisms, with levers, pulleys, and chemicals and feedback regulation at all levels. It is not, however, a machine built from blueprints created by an engineer. Instead, it is a jury-rigged system that generally works, despite serious “design” flaws such as the inside-out eye and the double curve in the spine (57). Its complexity goes far beyond complexity we can readily describe, because it emerged from layer on layer of systems built from tiny variations over hundreds of millions of years. Many wish it was easy to map modules in the brain to specific functions, but we are finding functions distributed among various areas in ways that defy common sense and any ability to come up with a clear description (58). We strive to characterize the function of a gene, only to discover that most do more than one thing, and some have very different functions depending on the tissue and the phase of development. Thus, as Barton Childs pointed out so well, the body is not a designed machine; it is a soma shaped by selection, and that is something very different (47). As students become increasingly able to understand the limits of the designed machine metaphor, and as they grasp the body as a product of natural selection, they will have a deeper understanding of the body, and why it is vulnerable to disease.

Implementation

At the Sackler Colloquium, leaders from Harvard, Yale and Johns Hopkins discussed plans to incorporate evolutionary biology into their medical curricula. Other institutions are making

similar efforts. Some countries, such as Norway, seem to be ahead (59), while the UK faces different challenges (60). Variations among such plans will soon reveal what works better and not so well, and curricula will evolve. As is the case for a rare beneficial allele, however, the initial spread is the risky part. We offer several suggestions to ensure that the current momentum continues, and some thoughts about how to get initial efforts going in healthy directions.

First, additional formal investigations into the role of evolutionary biology in medical and public health curricula are needed. Our opinions, however considered, are no substitute for the conclusions of diverse groups of experts convened to address these issues. We hope the AAMC, perhaps in conjunction with the HHMI, the IOM and a major scientific society of evolutionary biologists, will convene groups to address this issue.

Second, new teaching materials are needed for premedical and medical curricula. Some are newly available (27, 28, 61), but it is important to recognize that these efforts are early; developing a selection of teaching materials will take time. Free web-accessible educational resources would be very helpful.

Third, with curricula already overly full, and without evolutionary biologists on the faculty, few medical schools are positioned to take advantage of these opportunities. Strong leadership will be essential. Creating new courses and integrating cogent evolutionary examples into existing courses will also be essential. Time for needed new courses will have to come from existing courses, but it is difficult to get disciplines to give up teaching time no matter how compelling the case for new content. Some initial implementations will likely be by Dean's decision, but perhaps some faculties will cooperate to take advantage of the opportunity. The incorporation of evolutionary content in existing courses, done well, should recruit support for finding time to give students the basics early in medical school.

Fourth, we recommend that the impact of implemented changes be subject to rigorous investigation from the start. This will require careful research designs to measure the knowledge and performance of students who have and have not received teaching about evolutionary

applications in medicine. In addition to measuring knowledge about evolution and its medical applications, we suggest measuring changes in their ability to explain diseases to patients, their ability to evaluate evolutionary hypotheses critically, their ability to integrate knowledge from diverse sources, and the degree to which they attain a “feeling for the organism,” that informs their intuition about conditions they have not specifically studied.

Implementation could be accelerated by the simple and overdue action of including questions about evolutionary biology on medical certification examinations at all levels. The MCAT will soon include questions about evolutionary biology. Step 1 of the US Medical Licensing Examination includes questions from each of the traditional basic sciences for medicine, but does not cover content related to evolutionary biology. Students know they need to learn details about anatomy, physiology, and biochemistry to become certified. No such questions ensure that physicians understand the principles of evolutionary biology. We recommend adding such questions.

Conclusion

One hundred and fifty years after publication of *The Origin of Species*, new advances demonstrate the utility of evolutionary biology in medicine, but few physicians and medical researchers have taken a course on evolutionary biology, and no medical school teaches evolutionary biology as a basic science for medicine. It is as if engineering students never learned physics.

Filling this gap will require substantial changes in medical education policies and practices. Our suggestions about content, and when and how best to teach it, are only a beginning. National and international organizations such as the American Association of Medical Colleges, the Institute of Medicine, the Howard Hughes Medical Institute, and the Wellcome Trust have crucial roles to play in deciding what evolution education is needed, how to provide it, and how to implement it. A private foundation could, for a remarkably small investment, have a major impact on the future of medicine. Many physicians, researchers, and educators stand ready to help do what needs to be done so that human health gets full benefit from the basic science of evolutionary biology.

References

1. Futuyma D (2001) Evolution, science, and society. *Am Nat* 158 Suppl 4:S1-46.
2. Stearns SC & Hoekstra RF (2005) *Evolution : an introduction* (Oxford University Press, Oxford [England] ; New York) 2nd Ed.
3. Futuyma DJ (2005) *Evolution* (Sinauer Associates, Sunderland, Mass.).
4. Felsenstein J (2004) *Inferring Phylogenies* (Sinauer Associates, Sunderland, Mass).
5. Williams GC (1966) *Adaptation and natural selection; a critique of some current evolutionary thought* (Princeton University Press, Princeton, N.J.).
6. Wright S (1932) The roles of mutation, inbreeding, crossbreeding and selection in evolution. *Proceedings of the 6th International Congress of Genetics* 1:356-366.
7. Tinbergen N (1963) On the aims and methods of ethology. *Zeitschrift fur Tierpsychologie* 20:410-463.
8. Mayr E (1974) Teleological and teleonomic, a new analysis. *Boston Stud. Philo. Sci.* 14:91-117.
9. Williams GC (1957) Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution* 11(4):398-411.

10. Kirkwood T & Austad S (2000) Why do we age? *Nature* 408(6809):233-238.
11. Fisher RA (1930) *The genetical theory of natural selection* (The Clarendon press, Oxford, UK).
12. Williams GC (1975) *Sex and evolution* (Princeton University Press, Princeton, N.J.).
13. Stearns SC (1987) *The Evolution of sex and its consequences* (Birkhäuser Verlag, Basel ; Boston).
14. Hurst LD (1995) Selfish genetic elements and their role in evolution: the evolution of sex and some of what that entails. *Philos Trans R Soc Lond B Biol Sci* 349(1329):321-332.
15. Greaves MF (2000) *Cancer: The Evolutionary Legacy* (Oxford University Press, Oxford ; New York).
16. Low BS (2000) *Why Sex Matters* (Princeton University Press, Princeton, NJ).
17. Stearns SC (1992) *The evolution of life histories* (Oxford University Press, Oxford England ; New York).
18. Hill K & Hurtado A (1991) The evolution of premature reproductive senescence and menopause in human females. *Hum Nat* 2(4):313-350.

19. Hamilton WD (1964) The genetical evolution of social behavior I, and II. *J Theor Biol* 7:1-52.
20. Hammerstein P (2003) *Genetic and Cultural Evolution of Cooperation* (MIT Press in cooperation with Dahlem University Press, Cambridge, Mass.).
21. Kruger DJ & Nesse RM (2006) An Evolutionary Life-History Framework for Understanding Sex Differences in Human Mortality Rates. *Hum Nat* 17(1):74-97.
22. Pollard T (2008) *Western Diseases: An Evolutionary Perspective* (Cambridge University Press, Cambridge).
23. Nesse RM (1990) Evolutionary explanations of emotions. *Hum Nat* 1(3):261-289.
24. Nesse RM (2005) Natural Selection and the Regulation of Defenses: A Signal Detection Analysis of the Smoke Detector Principle. *Ev Hum Behav* 26:88-105.
25. Trevathan WR, McKenna JJ, & Smith EO eds (2007) *Evolutionary Medicine, Second Edition* (Oxford University Press, New York).
26. Nesse RM & Stearns SC (2008) The great opportunity: Evolutionary applications to medicine and public health. *Evol Appl* 1(1):28-48.
27. Stearns SC & Koella JK eds (2007) *Evolution in Health and Disease, Second Edition* (Oxford University Press, Oxford).

28. Gluckman PD, Beedle A, & Hanson MA (2009) *Principles of evolutionary medicine* (Oxford University Press, Oxford ; New York).
29. McVean G & Spencer CC (2006) Scanning the human genome for signals of selection. *Curr Opin Genet Dev* 16(6):624-629.
30. Sabeti PC, *et al.* (2006) Positive natural selection in the human lineage. *Science* 312(5780):1614-1620.
31. Li H, *et al.* (2008) Ethnic Related Selection for an ADH Class I Variant within East Asia. *PLoS ONE* 3(4):e1881.
32. Crespi B & Badcock C (2007) Psychosis and autism as diametrical disorders of the social brain. *Behav Brain Sci.*
33. Baer CF, Miyamoto MM, & Denver DR (2007) Mutation rate variation in multicellular eukaryotes: causes and consequences. *Nat Rev Genet* 8(8):619-631.
34. Muller HJ (1950) Our load of mutations *Am J Hum Genet* 2:111-176.
35. Weiss KM (2008) Tilting at Quixotic Trait Loci (QTL): An Evolutionary Perspective on Genetic Causation. *Genetics* 179(4):1741-1756.
36. Proctor RN (1988) *Racial Hygiene: Medicine Under the Nazis* (Harvard University Press, Cambridge, MA).

37. Zampieri F (in press) Medicine, evolution and natural selection: An historical overview. *Q Rev Biol*.
38. Alters B & Nelson C (2002) Perspective: Teaching evolution in higher education. *Evolution* 56(10):1891-1901.
39. Ewald PW (1994) *Evolution of infectious disease* (Oxford University Press, Oxford [England] ; New York).
40. Nesse RM & Williams GC (1994) *Why we get sick : the new science of Darwinian medicine* (Times Books, New York).
41. Stearns SC & Ebert D (2001) Evolution in health and disease. *Q Rev Biol* 76(4):417-432.
42. MacCallum CJ (2007) Does Medicine without Evolution Make Sense? *PLoS Biol* 5(4):e112.
43. Colleges AAoM & Institute HHM (2009) Scientific Foundations for Future Physicians.).
44. Nesse RM & Schiffman JD (2003) Evolutionary Biology in the Medical School Curriculum. *BioScience* 53(6):585-587.
45. Downie JR (2004) Evolution in health and disease: The role of evolutionary biology in the medical curriculum. *Biosci Ed Elect J* 4(November):1-18.

46. Nesse RM & Williams GC (1997) Evolutionary biology in the medical curriculum: What every physician should know. *BioScience* 47(10):664-666.
47. Childs B, Wiener C, & Valle D (2005) A science of the individual: Implications for a Medical School Curriculum. *Annu Rev Genomics Hum Genet* 6:313-330.
48. Harris EE & Malyango AA (2005) Evolutionary explanations in medical and health profession courses: are you answering your students' "why" questions? *BMC Med Educ* 5(1):16.
49. Perlman RL (2005) Why disease persists: an evolutionary nosology. *Med Health Care Philos* 8(3):343-350.
50. Nesse RM (2005) Maladaptation and natural selection. *Q Rev Biol* 80(1):62-70.
51. Valle D & Eyre-Walker (in press) *PNAS*.
52. Houle D (in press) Phenotypic selection. *PNAS*.
53. Williams GC (1996) *Adaptation and natural selection : a critique of some current evolutionary thought* (Princeton University Press, Princeton, N.J.).
54. Dawkins R (1989) *The Selfish Gene* (Oxford University Press, Oxford ; New York) New Ed.

55. Charlton BG (1997) A syllabus for Evolutionary Medicine. *J R Soc Med* 90:397-399.
56. Avise JC & Ayala FJ (2009) In the light of evolution III: Two centuries of Darwin. *Proceedings of the National Academy of Sciences* 106(Supplement 1):9933-9938.
57. Held LI (2009) *Quirks of human anatomy : an evo-devo look at the human body* (Cambridge University Press, Cambridge ; New York).
58. Pessoa L (2008) On the relationship between emotion and cognition. *Nat Rev Neurosci* 9(2):148-158.
59. Myserud I (1998) The history, status and teaching of Darwinian medicine in Norway. *Norsk Epidemiologi* 8(1):101-108.
60. Elton S & O'Higgins P (2008) Is There a Place for Evolutionary Medicine in UK Medical Education? *Medicine and Evolution: Current Applications, Future Prospects*, (CRC Press, Boca Raton, FL), Vol 48, 257-269.
61. Nesse RM (2007) Evolution and Medicine:How New Applications Advance Research and Practice. in *Henry Stewart Talks*, ed Nesse RM (Henry Stewart, Inc.).

